ON THE INHERITANCE OF THE ENZYMATIC ACTIVITIES OF LACTATE DEHYDROGENASE AND MALATE DEHYDROGENASE IN HUMAN ERYTHROCYTES

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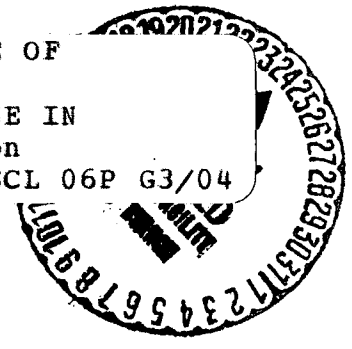

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ABSTRACT. Activities of the enzymes lactate dehydrogenase and malate dehydrogenase were determined in erythrocyte hemolysates from 20 families with 40 adults and 35 children. Agreement of the enzyme activities for the genetically different parents was found in 30% of the cases for lactate dehydrogenase and in 45% of the cases for malate dehydrogenase. Of the 35 children, the relations did not vary by more than 10% in 63% for lactate dehydrogenase and in 68% for malate dehydrogenase. The question of genetic or metabolic dependence of the variability of enzyme activities was discussed.

In recent decades, a whole series of inherited metabolic diseases with /10* enzyme defects have become known [6, 10, 13, 15]. Conversely, one can conclude from this that "normal" enzyme activities can be inherited for most metabolically healthy humans. The enzymatic machinery of the cells differs, according to the functional differentiation of the individual tissues [11]. For example, enzymes which are functionally part of the glycolytic chain are adjusted to each other in groups of constant proportions [1-3]. The intracellular enzyme activities are changed by a great number of biochemical factors, such as hormones [4, 5, 7, 14, 16], as well as by pathological states [12]. The magnitude of the range for physiological variations of the enzyme activities of morphologically equivalent cells under the same external conditions is not known, because it is always only an average which is obtained by determining the /11 activities in tissue homogenates.

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*Numbers in the margin indicate the pagination in the original foreign text.

We consider the erythrocytes to be suitable objects from which to draw conclusions about the hereditary transmission of certain enzyme activities through family investigations. The external similarity of family members could correspond to a basic similarity of cell structure, and the red cells have lost the capability for production of new enzymes.

Materials and Methods

Citrated venous blood obtained in blood donation activities was used for the studies. The children were brought by their parents for determining blood grouping.

Approximately 10 ml of venous blood were collected in standard centrifuge /13
tubes. Each tube contained 38 mg dry sodium citrate to prevent clotting. Enzyme activities were determined within 48 hours of the time blood was drawn, since the blood was brought even from distant locations in special cold containers. The sedimented erythrocytes were washed three times on the centrifuge with 0.9% sodium chloride solution. One milliliter of erythrocyte suspension was hemolyzed with double-distilled water. The hematocrit was determined simultaneously. The enzyme activities in the hemolysate were determined with the test combinations of the Boehringer, Mannheim Company[1]. The measured enzyme activities were expressed in relation to one millimeter of hematocrit. The photometric determination of the enzyme activities was done partly with a Beckman spectrophotometer and partly with an Eppendorf photometer having a thermostatted cuvette holder and linearizing direct recorder.

Results and Discussion

Sex, age, and degree of relationship are shown in Table 1, with the activities found for lactate dehydrogenase and malate dehydrogenase. The

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[1]We thank Boehringer and Sons, Mannheim, for financial support.

TABLE 1. NAME, SEX AGE IN YEARS, AND ACTIVITIES OF LACTATE DEHYDROGENASE AND MALATE DEHYDROGENASE IN ERYTHROCYTE HEMOLYSATE PER MILLIMETER OF HEMATOCRIT. V/M = RELATION: FATHER/MOTHER, V/K = RELATION: FATHER/CHILDREN, M/K = RELATION: MOTHER/CHILDREN, K/K = RELATION: CHILD/CHILD. A RELATION IS POSITIVE, +, IF THE ENZYME ACTIVITY VARIES BY NO MORE THAN 10% FROM THE LOWER TO THE COMPARISON VALUE.

(LDH = lactate dehydrogenase, MDH = malate dehydrogenase)

Nr.	Name	♂ ♀	Age	LDH	V/M	V/K	M/K	K/K	MDH	V/M	V/K	M/K	K/K
1	N. P.	♂	39	560	—	—	+	—	370	+	+	+	—
	N. A.	♀	36	690		+	—		370		—	—	
	N. J.	♀	7	640					400				
	N. E.	♀	4	530					470				
2	B. G.	♂	42	520	—	+	—	—	390	—	+	—	+
	B. T.	♀	42	470		—	+		320		+	—	
	B. H.	♂	17	530					380				
	B. G.	♀	11	470					390				
3	K. K.	♂	44	240	—	—	—	—	440	+	—	—	+
	K. E.	♀	41	570		—	—		480		—	—	
	K. C.	♀	16	510					570				
	K. H.	♀	14	280					610				
4	W. W.	♂	49	440	—	—	+	—	580	—	—	+	—
	W. J.	♀	49	490		—	—	—	660		—	—	—
	W. H.	♀	23	500		+	+		670		—	+	—
	W. J.	♀	19	680					670				
	W. H.	♂	10	450					580				
5	S. O.	♂	38	420	—	—	—	—	410	—	—	+	+
	S. M.	♀	39	490		—	+	—	500		—	+	+
	S. K.	♂	11	610		—	—	—	510		—	+	+
	S. E.	♂	7	510					520				
	S. W.	♂	6	680					550				
6	L. W.	♂	43	720	—	—	—	—	360	+	—	—	—
	L. F.	♀	43	860		—	+		360		+	+	
	L. H.	♂	14	1130					410				
	L. N.	♂	12	860					370				
7	M. B.	♂	44	500	+	+	—	+	820	—	—	—	—
	M. M.	♀	33	550		+	—		630		—	+	
	M. W.	♀	16	490					570				
	M. A.	♀	13	490					690				
8	H. W.	♂	52	260	—	—	+	—	640	+	+	+	—
	H. M.	♀	45	370		—	—		610		+	—	
	H. M.	♂	22	370					650				
	H. R.	♀	21	630					700				

TABLE 1. (Continued)

/12

Nr.	Name	♂ ♀	Age	LDH	V/M	V/K	M/K	K/K	MDH	V/M	V/K	M/K	K/K
9	M. J.	♂	30	320	+	+	+	—	510	—	+	—	+
	M. G.	♀	26	340		—	—		700		+	—	
	M. W.	♂	7	350					480				
	M. M.	♀	6	390					480				
10	K. F.	♂	40	490	—	—	—	—	350	—	—	—	—
	K. A.	♀	40	590		—	+		440		—	+	
	K. K.	♂	12	710					540				
	K. B.	♀	10	620					420				
11	K. O.	♂	39	350	+	—	+	+	410	+	—	+	+
	K. H.	♀	38	380		—	+	—	450		+	+	+
	K. G.	♂	8	400		—	—	—	460		+	+	+
	K. R.	♀	8	400					450				
	K. E.	♂	4	570					450				
12	S. H.	♂	38	890	+	+	+		360	—	+	+	
	S. H.	♀	39	920					400				
	S. K.	♀	9	890					370				
13	S. C.	♂	38	420	+	+	+	+	590	+	+	+	+
	S. H.	♀	40	420		—	—		580		—	—	
	S. W.	♂	9	460					630				
	S. D.	♀	7	480					650				
14	S. K.	♂	36	740	—	+	—		520	—	+	—	
	S. J.	3	31	650					450				
	S. H.	♂	7	790					520				
15	S. W.	♂	47	410	—	+	—		570	—	—	—	
	S. K.	♀	37	740					700				
	S. H.	♂	10	410					500				
16	M. H.	♂	34	470	—	+	—		490	+	—	+	
	M. B.	♀	36	340					440				
	M. D.	♂	12	440					420				
17	F. E.	♂	40	1290	—	—	+		570	—	—	—	
	F. E.	♀	38	860					450				
	F. J.	♀	10	820					300				
18	J. J.	♂	44	350	—	—	+		620	+	+	+	
	J. M.	♀	43	570					680				
	J. R.	♂	15	530					630				
19	S. G.	♂	50	820	+	—	—		330	+	—	—	
	S. H.	♀	43	820					330				
	S. T.	♂	3	1010					430				
20	B. R.	♂	33	780	—	—	+		500	—	+	+	
	B. M.	♀	28	550					450				
	B. K.	♂	10	550					480				

members of 20 families, totalling 75 persons, were studied. The enzyme activities, rounded off to tens of Wroblewski Units, were considered in agreement if the values were the same, or if they varied no more than 10% from the lower to the comparative value. Such a relation is designated as positive. We consider the mean difference of 10% between the values found as the probable range of error for the method, on the basis of duplicate determinations. The father:mother comparison, i.e., for persons who are not blood relatives, was positive for lactate dehydrogenase in 30% of the cases, and for malate dehydrogenase in 45% of the cases. The father:children relation showed essentially the same results, while the mother:children relation was greater with lactate dehydrogenase = 46% and malate dehydrogenase = 51% (see Table 2). Of the 35 children studied, 22 (63%) agreed with one of the parents for lactate dehydrogenase, and 24 (68%) agreed for malate dehydrogenase. We have omitted a more thorough statistical breakdown because some data are still unknown.

TABLE 2. RELATIONSHIPS AND COMPARISON OF THE ACTIVITIES OF LACTATE AND MALATE DEHYDROGENASE. TWENTY FAMILIES STUDIED, WITH SEVENTY-FIVE PERSONS. PARENTS: 20 FEMALE, 20 MALE
CHILDREN: 16 FEMALE, 19 MALE

Relations		Lactate dehydrogenase				Malate dehydrogenase			
	Number	negative	%	positive	%	negative	%	positive	%
Father/mother	20	14	70	6	30	11	55	9	45
Father/children	35	24	68	11	32	19	54	16	46
Mother/children	35	19	54	16	46	17	49	18	51
Child/child	18	15	83	3	17	7	39	11	61
Parents/children	70	43	62	27	38	36	51	34	49

The measured activities show a considerable range of variations. For the lactate dehydrogenase, the extreme values were 240 and 1290 Wroblewski units

per millimeter of hematocrit. For malate dehydrogenase, the extreme values were 300 and 820 units. The more frequent agreement of the values found for malate dehydrogenase, in comparison to lactate dehydrogenase, may at least in part be due to that. With variation of the physiological values by some 100%, agreement in 30 - 60% of the values is striking. Comparisons between the children showed quite different results for lactate dehydrogenase and malate dehydrogenase. We are unable to say whether this is due to chance because of the small numbers, or to some other cause. The two enzymes showed positive or negative relations between relatives, independently of each other. /14

This high scattering of activities can have various causes:

1. In the maturation of the erythrocytes, they receive an average amount of enzyme protein per blood cell, and the activity per milligram enzyme is variable within wide limits due to activators or inhibitors.
2. Different, genetically determined amounts of enzyme are provided to the blood cells of different individuals, and the corresponding activity per milligram of enzyme protein varies in more or less narrow limits.

Certainly, in the final expression of the enzyme activities, not only genetic factors but also metabolically conditioned effects play a role [4, 5, 7-10, 13, 14]. The more frequent agreement in the mother/children relation, which is apparent in Table 2, could be genetically determined, but it could also be due to the usual great similarity in the nutrition of the mother and children. To answer the questions from this work, two other component questions must be explained:

1. Within what limits can the erythrocytic enzyme activities vary under physiological conditions, and how great are the changes under pathological conditions. This question relates to physiological activators or inhibitors.

2. If there are in fact different genes which determine the enzyme amounts and activities in the cells, how is the gene distributed within the population, and what is the mode of transmission.

Future studies must consider the isoenzymes present, the water content of the erythrocytes, and other data.

Illegitimate children represent a source of error which is difficult to realize. There is another difficulty due to the fact that in Germany large families with many children, which are of interest in this relation, are very rare.

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